SERIES

Research governance: regulating risk and reducing harm?

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This is the second in a series of three papers on research governance. [Series editors: Trisha Greenhalgh and Sara Shaw]

SUMMARY

Risk assessment can be thought of as the lens through which we anticipate the consequences of research and the impact of the actions of researchers. The way in which risk of harm is managed in research is strongly influenced by the surrounding social and political environment, leading to differences in national and local styles of regulation and review.

Different research studies carry different risks, so systems for review and approval must adapt to the question being asked and the nature of the study. Researchers can never wholly guarantee safety in any research but participants and researchers must be offered reasonable protection within any study, with appropriate arrangements in place should something go wrong.

INTRODUCTION

The past 20 years have witnessed the development of a more systematized approach to research, with greater emphasis on accountability, performance management, and quality assurance. The review of research now involves interpreting layers of complex legislation and assessing whether the potential benefits of a particular research project in terms of important knowledge gained are proportionate to the potential physical and/or psychological harm it might cause. However, efforts to articulate this in the design, conduct and management of research have revealed deep divisions around how to define and apply concepts of minimal risk, potential benefit and important knowledge.

In this paper, we explore the risk of harm within research, the means by which this is regulated and the impact on researchers. Paper three in this series describes how risk can be effectively communicated to potential research participants.

WHAT IS RISK?

Risk is broadly concerned with potential—but not precisely knowable—harm. It is a concept that is pervasive in modern Western society and, despite a growing literature on public views of risk, is most often articulated in terms of calculation, measurement, probability and the prediction of potential adverse events (having been based in earlier times on notions of fate or chance). This approach is grounded in a rational, post-Enlightenment view of the world, where potential harm is assessed using mathematical judgements to weigh up potential risks and benefits.[1,2] Such judgements are not value free. They are based on interpretation of the scientific evidence about the risk of harm to research participants[2,3] and may be influenced by high-profile events that provide impetus for government or professional intervention.[4] For instance, despite the evidence that many of the actions taken prior to the Alder Hey organ retention scandal were within legal and ethical codes of the time, the high-profile and controversial nature of subsequent debate resulted in changes in the way in which surgical or autopsy tissue is stored.[5,6]

Researchers now work within what has been termed a 'risk society',[7] characterized by social and technical advances but with limited knowledge regarding related risks (such as those associated with unknown latent infection following xenotransplantation). In seeking to cope with this phenomenon, modern society has become increasingly concerned, not only with the risk of harm, but with the assessment, management, communication and monitoring of that risk.[7,8] However, not only is the concept of risk historically and socially located (i.e. it is perceived in different ways by different people and across different societies[1]), there is also little evidence that the extensive arrangements in place for assessing and managing risk are effective.

Risk is therefore not a blanket term to be applied in the same way across all studies. This is evident in the UK Research Governance Framework, which states that some standards for managing risk in research may require judgement and interpretation.[9] Good governance structures and systems therefore provide a framework for action rather than prescriptive protocols.

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Box 1 **Evidence of harm in research**

NEGLIGENT OR DELIBERATE HARM (a good researcher would have avoided it)	
Fraud and misconduct	A number of cases have been documented of the deliberate modification or fabrication of data, such as that of William Summerlin who used a felt-tip pen to fake a successful skin transplant from a black mouse to a white one.[11] Other cases include plagiarizing information or using inappropriate controls in trials.[11] All of which carry a risk of harm due to future decision-making regarding care being based on incorrect or misleading findings
Loss of benefit	The use of placebo in trials where treatments are known to exist continues to be debated with the risk of harm expressed as potential loss of benefit due to being deprived of access to treatment. Examples include the use of placebo controls in psychiatric research,[12] trials of AIDS products in developing countries and in trials for conditions such as mild hypertension or asthma[13]
Withdrawal of medication	Some studies have deliberately withdrawn medications prescribed for a therapeutic purpose in order to study the effects or to initiate another therapy: the risk of harm resulting from such studies may include exacerbation of symptoms, prolonging the condition and emotional or physical suffering[12]
Straying from the research protocol; poor science	A US professor of psychiatry was found to be negligent having deviated from 'accepted practices in the conduct and reporting of science'. Records from the drug trial in which he was involved showed some allegedly healthy (or normal) controls to be suffering from mild senile dementia.[11] This carries a risk of harm as future care or health status may be affected by inaccurate information
NON-NEGLIGENT OR UNINTENDED HARM (could happen to anyone)	
Adverse drug reactions	In phase-I drug trials estimates indicate around 3% of adverse events are severe, including incidences of loss of consciousness, atrial fibrillation and hyperthyroidism.[14] Although exceptional, some research carries the risk of life-threatening adverse events
Non-deliberate but adverse outcome due to study design	A recent non-intervention study of patients awaiting coronary artery bypass surgery considered a range of ethical issues relating to study design and received approval for this from the relevant ethics committee. However, 4 of the 70 participants died, leading to changes in the research protocol and subsequent intervention by the researcher where participants' clinical condition had worsened[15]
Non-deliberate violation of research norms and regulations	Having gained the necessary approvals, a recent questionnaire study exploring day therapy services for eating disorders subsequently sought to undertake an additional qualitative arm. Unaware of new requirements, researchers incorporated this into the protocol without informing the relevant committees and without adding it to the patient information and consent forms, despite it needing to be reassessed by the committee in light of the new methods adopted and related ethical issues[16]

HOW IS THE RISK OF HARM ASSESSED?

As with every activity, research inevitably carries some risk (see Box 1).[10] In the same way that there are a number of assumed risks that we sign up to in our daily lives (for instance, in getting on a bus, we implicitly accept the risk of a road accident), researchers can never wholly guarantee safety and participants must therefore be aware of the risks and accept them before taking part in the research. Harm can be either unintentional (also referred to as non-negligent) or negligent. Whereas non-negligent harm might be regarded as bad luck or one of the risks we all live with (for example slipping over and breaking your ankle while attending for a sight test); negligent harm involves some level of culpability (for example, on the part of a nurse who administers a dirty needle when taking blood and is later faced with a patient infected with Hepatitis B). Risk assessment goes some way to addressing negligent harm (by, for instance, identifying likely incidents of fraud and misconduct) and offers a means of minimizing the potential for non-negligent harm (by, for instance, ensuring that individuals are properly selected, trained and supervised and keep auditable records).

The processes of review undertaken by research ethics and governance committees provide a framework for assessing the risk of harm potentially brought about by research studies and ensuring that this is proportionate to the potential benefit(s) to be gained. In terms of thinking about the potential harms of research, local and multicentre research ethics committees draw upon a range of ethical frameworks and guidelines (see paper one for detailed list), all of which were developed primarily around the clinical drug trial. As a result, the concept of risk has typically been expressed in terms of the physical, moral and emotional harm associated with drug interventions and associated tests and monitoring procedures.

Box 2 **Sources of advice and guidance***

ASSESSING RISK

- The *Primary Care Trust Research Management & Governance toolkit* (provided by the NHS R&D Forum) includes information relating to establishing shared arrangements and sharing risk and is available from http://www.rdforum.nhs.uk/toolkit.htm
- The NHS Litigation Authority publish a risk management strategy at http://www.nhsla.com/NR/rdonlyres/A833203F-8DE8-4B96-A152-F8A63203C4D7/0/RiskManagementStrategyver7approved.doc
- The NHS R&D Forum have also produced guidance on developing procedures within NHS organizations for appropriate authorization and management of research and related projects available from http://www.rdforum.nhs.uk/docs/categorising_projects_guidance.doc

LEGAL ISSUES

- The full text of the *Human Tissue Act* is at http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm
- The Medicines and Healthcare Products Regulatory Agency has a link to the *EU Clinical Trials Directive* (2001/20/EC), as well as other useful information and guidance, available from http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/clintrialdir.htm
- The full text of the *Data Protection Act* (1998) is available from http://www.hmso.gov.uk/acts/acts1998/19980029.htm
- The full text of the *Human Fertilisation and Embryology Act* is available at http://www.hmso.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm
- The full text of the *Health and Social Care Act* is at http://www.legislation.hmso.gov.uk/acts/acts2001/20010015.htm and the sections relevant to patient information are 60 and 61.

INDEMNITY AND INSURANCE

- The NHS Litigation Authority indemnifies NHS bodies in respect of clinical negligence and non-clinical risks and manages claims and litigation for both http://www.nhsla.com/home.htm. The website provides a useful summary of applicability of NHS indemnity to common situations, as well as an annex on sponsored trials (refer to *NHS Indemnity: Arrangements for Clinical Negligence Claims in the NHS*)
- Those concerned about indemnity arrangements for within primary care should refer to a joint statement from the NHS R&D Forum, UK Federation of Primary Care Research Organisations and the Society of Academic Primary Care available at: http://www.rdforum.nhs.uk/workgroups/primary/indemnity_arrangements.doc

ACCESSING PATIENT DATA

- Guidance on the application of the Data Protection Act is provided by the Information Commissioner at http://www.informationcommissioner.gov.uk/cms/DocumentUploads/Use%20and%20Disclosure%20of%20Health%20Data.pdf. Other legal guidance, is also available from the Information Commissioners office at www.informationcommissioner.gov.uk
- The Department of Health publishes an *NHS Code of Practice on Confidentiality* (published in 2003), available through their website at http://www.dh.gov.uk
- The Patient Information Advisory Group website is at http://www.advisorybodies.doh.gov.uk/piag/ where the annual report and guidance can also be found.

*Refer to the first paper in the series for details of (and links to) regulations and guidance relating to healthcare research

Actual evidence about the harms of research is fairly thin on the ground, particularly for non-intervention studies. Assessing the potential benefit of a proposed study is an even more difficult task. For example, research involving human gene transfer carries formidable challenges to ethics committees trying to evaluate proportionality of risk and benefit without any way of knowing the actual (as opposed to expected) impact the work will have in the future.

Because ethical frameworks and guidelines necessarily need to be interpreted, and because evidence on the potential harms of research is invariably incomplete, committees have to make judgements, often on a case-by-case basis. Over time, they may also develop patterns of custom and practice—a fact that partly explains the variation that researchers can experience between committees.[17,18]

Although non-intervention studies such as survey research or participatory action research are not devoid of risks, there has been a recent trend towards greater consideration of the potential harms of such studies.[19] Ironically, this approach carries some risk of its own by imposing inappropriate or inflexible frameworks of ethical evaluation. For example, there is a danger of over-emphasizing risks[20] or imposing requirements (e.g. written consent), which may fit poorly with the research design.[21] It is beginning to be acknowledged that a more flexible review and approvals' procedure would probably lead to greater benefits overall. The NHS R&D forum has already begun exploring this issue (Box 2).

An unintended consequence of the system has been to block or hinder research studies that do not really have unresolved ethical issues, through either delays[20] or committees' conservative judgements.[18] Although the protection of participants (particularly 'vulnerable groups'[19] such as children or the mentally incapacitated) from physical and psychological harm is the *raison d'être* of ethics committees, there is a paucity of research about the extent of protection needed. Two recent studies have strongly suggested that ethics committees' assumptions about the vulnerability of certain groups may not always be in

Box 3 **Roles and responsibilities and liabilities in research**

Individual or organization	Roles and responsibilities
Grant holder (also known as Principal Investigator or Chief Investigator)	Professional role largely defined by accountability for research project(s) and supervision of any staff/students involved. They are accountable for conducting research to the agreed protocol and in accordance with legal requirements, including ethics and governance. The Chief Investigator has overall responsibility for a study, whereas the Principal Investigator has responsibility for the study at a particular site within a multi-centre study (also known as Local Investigator)
Steering Group Member	Directive role, asking questions about the purpose, progress and outcomes of a study. Not usually accountable for the research. May also be grant holder, and/or represent a local/national organization or service
Research Assistant	Task-oriented post involving, for instance, collecting data or interviewing participants. Research assistants may have responsibilities for data entry and cleaning, but possibly not for analysis
Analyst (e.g. statistician or qualitative researcher)	Either employed on a specific task basis to analyse/organize qualitative and/or quantitative 'data', or involved more substantively in the design and management of the research
Consumer (also known as user, patient, carer, etc.)	Generally someone who sits on a steering group and provides a user perspective but can fill many of the above roles and may be particularly important at design stage where they often second-guess a lot of ethical and consent issues
Research participant (also known as patient or subject, etc.)	Takes part in the research having received all the relevant information, had the opportunity to ask questions and then given their consent to do so. Participant is the preferred term, indicating active participation in the research process
Sponsor	Monitoring role, taking overall responsibility for the initiation, management and financing of a research project. Responsibilities relate to the conduct (rather than the scientific quality) of research and the monitoring of research governance arrangements. Sponsors often, but not always, provide indemnity cover for studies. It is now a legal requirement that all clinical trials falling under the *Medicines for Human Use (Clinical Trials) Regulations 2004* have a sponsor in place
Host organization	Either the organization in which a research project is actually based and managed (usually the employing organization); or the care organization(s) in which the research takes place
Employing organization	Employing role, promoting a quality research culture, ensuring researchers understand and discharge their responsibilities and that research is properly managed and monitored (where agreed with sponsor)
Care organization / responsible care professional	Broad assessment role, making sure that research taking place within the organization meets the standards set out in the Research Governance Framework and has ethics approval. Retains responsibility for research participants' care
NHS R&D or Research Governance Committee	Verifying role, ensuring that the proposed research meets the legal requirements of the Research Governance Framework. Registers and monitor research projects
NHS Research Ethics Committee	Ensures that the proposed research meets procedural requirements designed to protect the dignity, rights and well being of participants

step with the views of the 'vulnerable' individuals themselves.[22,23]

The involvement of multiple partners in research has the knock-on effect of potentially diffusing responsibility for any adverse effect on participants across organizations. As a result, this can accentuate perceptions of risk and lead to more stringent regulations within collaborative agreements.[3] UK governance arrangements attempt to address this by requiring delineation of research responsibilities and ensuring these are not only documented, but also communicated to potential research participants. Box 3 outlines key areas of accountability, which also, importantly, indicate potential liability.

LEGAL ISSUES

As well as research being *ethical*, it must also be *legal*. In the UK, NHS R&D committees are responsible for ensuring that the research carried out within the NHS is legal. Universities also have a responsibility to ensure that research carried out under their auspices is legal. In contrast, although NHS ethics committees must have due regard for the requirements of relevant regulatory agencies and applicable laws, they are required to pass opinion on the ethical acceptability of a project, rather than specific interpretation of regulations or laws.[23] In the UK there are a number of laws that researchers, R&D committees, and universities must be aware of (see Box 4).

Box 4 **Key legal requirements in research** (see Box 2 for web links)

The *Human Tissue Act*[5] introduced legislation in 2004 to regulate the removal, storage and use of human organs and tissue. As well as streamlining and up-dating existing law, the Act aimed to provide safeguards and penalties to prevent a recurrence of the distress caused by retention of tissue and organs without proper consent. As a result, living patients must now consent to retention/use of their organs and tissue when this goes beyond diagnosis and treatment and there must be consent for removal, retention and use of tissue from people who have died (in the event that they die without expressing a wish, consent must be given by someone nominated by or close to them)

The *Medicines for Human Use (Clinical Trials) Regulations*[29] came into force on 1 May 2004 to implement the *European Union Clinical Trials Directive*[25]. The aim is to provide an environment for conducting clinical research that protects participants without hampering the discovery of new essential medicines and to simplify and harmonize the administration of clinical trials across EU Member States. As a result, anyone wishing to ascertain the efficacy or safety of a medicine in human subjects must obtain a clinical trial certificate

The *Data Protection Act*[31] seeks to strike a balance between individual's rights regarding information held about them and those with legitimate reasons for processing and using their personal information. Those processing personal information must comply with principles of good information handling (e.g. data must be processed for limited purposes; be adequate, relevant and not excessive; be accurate and up to date and not kept longer than necessary)

The *Human Fertilisation and Embryology Act*[32] provides a legal framework for everyone involved in fertility treatments, making provisions to license and monitor any research using human embryos, as well as the performance of fertility treatment clinics. An amendment in 2001 allows for the creation of embryos for therapeutic cloning research. The Act permits research on human embryos only for strictly defined purposes, and if the Human Fertilisation and Embryology Authority considers the research to be 'necessary and desirable'

The *Health and Social Care Act*[33] allows for the use of patients' medical information without their consent to support essential medical purposes that are in the interests of the wider public and where obtaining consent is impracticable. Disclosures of data to cancer registries and for the purpose of communicable disease surveillance have been approved

There is huge overlap between what is ethical and what is legal, but there are contested areas. There has been much debate about the requirements of the Data Protection Act and the common law on confidentiality in recent years.[25] Although the debate continues,[26,27] the result has been greater restrictions on the use of identifiable medical data in order to lessen the risk of a breach of confidentiality. Researchers who are not involved directly in patients' clinical care now must apply, after gaining ethical approval, to the Patient Information Advisory Group (a temporary quango set up by the 2001 Health and Social Care Act—see Box 4) in order to use identifiable data without NHS patients' explicit consent. Such uses include previously unremarkable activities such as identifying a sampling frame for a survey, compiling registry information,[28] linking existing datasets, or identifying suitable patients to invite them to take part in a research study.[26,28]

ARRANGEMENTS FOR INDEMNITY

The very nature of risk means that researchers can only offer *reasonable*, not absolute, protection to participants. In general, indemnity (or insurance) arrangements must be in place so that, in the event that anyone is harmed as a result of deliberate intent or failing to follow normal procedures (negligence),[9] those affected within a research study can receive compensation via appropriate channels. However, less provision is generally made for non-negligent harm. (See Box 1 for examples of negligent and non-negligent harm.) For instance, the NHS can only address negligent harm as the legal liability arising from NHS Trusts' Duty of Care towards patients (i.e. NHS cover is not available for non-negligent harm).

It is the role of ethics committees to decide whether or not a study can go ahead without a scheme of compensation for non-negligent harm. Although there are no legal requirements to incorporate such a scheme, committees will consider this on a case-by-case basis (though researchers may also wish to consider any moral responsibilities in this regard). In general, committees are less concerned with non-intervention studies where the risk of harm is *considerably* less (see above). Either way, the Research Governance Framework[9] requires that compensation arrangements for negligent and non-negligent harm are made clear to participants before a piece of research can commence (see paper three in this series). This is particularly important where the research involves multiple partners.

CONCLUSION

Consideration of the risk of harm is integral to high quality research (see Box 2 for links to further guidance on many of the issues raised). Ethics and governance committees involved in approving research have an important role in conceptualizing what constitutes harm, giving importance

to reducing risk to participants.[9,10,13] Influenced by public concern and anxiety over medical research, those reviewing research do so through the lens of modern 'risk society', tending to focus on technical assessments of the risk of harm. For researchers seeking approval there remain many unanswered questions such as: Who decides on risks? By what criteria? How do the reviewers account for their decisions? In addition, more complex judgements regarding the character, professional integrity and experiential judgement of the researcher are not explicitly included, though a face-to-face interview at an ethics committee is an opportunity for the researcher to demonstrate these qualities. Arguably, there is a greater need for the formal consideration of researchers' virtues (as well as technical procedures) within risk assessment and governance arrangements generally. Consideration of issues of trust might facilitate risk assessment by allowing committees to explicitly differentiate between different studies and settings. One way to begin to address this might be to understand better how the research process is conceptualized and risk is assessed in different settings.

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